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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/999,690	09/08/97	GUNZBURG W	GSF97-03A

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EXAMINER	
CLARK, D	
ART UNIT	**PAPER NUMBER**
1633	9

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Please find below and/or attached an Office communication concerning this application or pr ceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 08/999,690	Applicant(s) Gunzburg et al.
	Examiner Deborah Clark	Group Art Unit 1633

☐ Responsive to communication(s) filed on _____ .

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-25* is/are pending in the application.

Of the above, claim(s) _____ is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-25* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☒ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☒ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____ .

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *8*

☐ Interview Summary, PTO-413

☒ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

DETAILED ACTION

Priority

1. Acknowledgment is made of applicant's claim for priority based on PCT/EP96/01001, filed 03/08/96 under 35 USC 111, and foreign priority based on an application filed in Denmark on 03/09/95, DK-0243/95. It is noted, however, that applicant has not filed a certified copy of the either of the applications as required by 35 U.S.C. 119(b), and 35 USC 111.

Claim Rejections - 35 USC § 101

2. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

3. Claim 22 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claim 22 is directed to a host cell infected with a virion according to claim 11. Because the specification teaches using the virion to administer to animals, including humans, the host cell is reasonably interpreted to encompass a human being. Human beings are non-statutory subject matter. Insertion of the word isolated or cultured prior to the word cell in the claim would obviate this grounds for rejection.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-15 and 20-22 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making a vector comprising a coding sequence encoding a microbial peptide and using said vector in applications, *in vitro*, does not reasonably provide enablement for use of said vector in an animal, *in vivo*. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Claims 1-8 are directed to a vector for introducing DNA into a eukaryotic cell, subsequently for treating tumors, viral infections, bacterial infections, and fungal infections. Claims 9-10 are directed to a vector system comprising a vector such as that described above. Claim 11 is directed to a retroviral particle produced by the system of claim 10. Claims 12-13 are directed to a provirus produced by infecting target cells with the particle of claim 11. Claims 14-15 are directed to a method of introducing DNA into a cell population using the vector system of claim 9. Claim 20 is directed to the mRNA of the provirus of claim 12. Claim 21 is directed to the RNA of the vector of claim 1. Claim 22 is directed to a host cell infected with the provirus of claim 11.

The specification does not enabled one of skill in the art to use the claimed invention commensurate in scope with the claims. The nature of the invention is gene therapy with anti-

microbial peptides. The state of the art of using anti-microbial peptides for therapy *in vivo* is not well established. Animal experiments have indicated that some of these peptides may be useful in the clinical setting. However, the use of these peptides has not progressed to the clinical setting (see Boman, Ann. Rev. Immunol. Vol. 13, at page 83). They are degraded by proteolytic enzymes and nothing is known about their uptake in different tissues (see same cite). Also, the dosages have not been established and are critical at least for some of these peptides (see same cite). Thereby making the use of these peptides for therapy *in vivo* unpredictable.

The state of the art of gene therapy is in it's infancy. Clinical efficacy has not been demonstrated in any gene therapy protocol (see Verma et al., Nature Vol. 389, at page 239). A major problem is the ability to deliver genes efficiently and to obtain sustained expression (see Verma et al., page 239, col. 3). Once delivered high level expression of genes transferred may not be consistently achieved (see Orkin et al., page 9, ¶2), which demonstrates that the art of gene therapy is unpredictable.

The specification does not teach any dosages of vector that would lead to expression of the encoded peptide at a therapeutic level. Applicants state that high concentrations of the peptides may be necessary (see the specification page 3 line 3). Further, in order to use the invention in the clinical setting, the expression of the peptide should not be toxic to the patient. It is not clear how well the level of peptide would be regulated once transferred into the patient. The working examples set forth in the specification demonstrate construction of retroviral vectors carrying cecropin A or mellittin, infection of EJ (human bladder carcinoma cells) cells with the

vectors and the subsequent transplantation of the cells into nude mice, and an in vitro experiment demonstrating an effect upon HIV LTR controlled expression of luciferase. None of these working examples are correlatable to use of the claimed vector or methods for therapy *in vivo*. In the anti-tumor example cells were infected *in vitro* and then implanted into nude mice. In the clinical setting the patient would be divergent from the nude mouse because the immune system of the nude mouse is deficient. The patient would likely have a normal immune system. Further, the tumor would already be inside the patient such that deliver of the vector would not be in a controlled setting such as the *in vitro* setting. Based upon the art of gene therapy it is unknown as to whether the vector would be delivered to the appropriate cells and then taken up, posttranslationally modified appropriately, and then expressed to a sufficient level to induce a therapeutic response. In the anti-viral example, all experiments were done *in vitro*. The *in vitro* data is not correlatable to the *in vivo* environment because the *in vivo* environment is not controlled as is the *in vitro* setting. For instance, the types of cells, the presence of degrading enzymes, the immune system, etc. Further, the experiment used only the HIV LTR, operably linked to the luciferase gene, in the presence or absence of tat and measured only expression of luciferase. This measurement is not indicative of viral infection because the infection of HIV is a complex event. The virus comprises several overlapping reading frames which encode several proteins some of which the function is not known. Some of which have functions that are responsive to other proteins and some of which have functions which overlap. It is not clear as to whether an inhibition of expression from the LTR would actually affect the patient to a

therapeutic degree as each cell infected with the virus would need to be infected with the vector. Given the state of the art of gene therapy this is highly unlikely.

The breadth of the claimed invention is not enabled. The claims encompass a retroviral vector comprising a coding sequence encoding virtually any peptide. The claims recite "antimicrobial peptides or derivatives thereof". The term antimicrobial peptide is defined broadly in the specification to encompass any peptide (see page 9, lines 5-12) and further, a derivative is anything derived from that sequence, hence every residue could be changed such that the derivative bears no relationship to the peptide from which it was derived. Not any peptide would have an effect upon bacteria, fungi, viruses, and tumors as required by the claims. Applicants have demonstrated only cecropin A and melittin, however, applicants discuss other amphipathic/lytic peptides such as magainin, defensin, etc. No other peptides are enabled for use in the claimed invention. Applicants should limit the claims to include only the class of peptides discussed in the specification.

Therefore, given the nature of the invention, the state of the prior art, the lack of predictability found in the art, the amount of guidance set forth in the specification, the lack of correlatable working examples, and the breadth of the claims, the amount of experimentation required to practice the invention commensurate in scope with the claims is paramount and undue.

6. Claims 16-19 and 23-25 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the

invention. Claim 16 is directed to a method for introducing nucleotide sequences into a mammal comprising infecting the mammal with a retrovirus produced by the vector system of claim 9. Claims 17-18 are directed to use of the vector of claim 1 or the vector system of claim 9, respectively, for producing a pharmaceutical composition for gene therapy. Claim 19 is directed to a pharmaceutical composition containing the particle of claim 11. Claims 23-25 are directed to methods for the treatment of a disease comprising administering to a subject a retroviral particle.

Each of the recited claims requires the use of a vector according to the invention for *in vivo* therapy. The specification does not enable one of skill in the art to use the invention as claimed as discussed above.

Therefore, given the nature of the invention, the state of the prior art, the lack of predictability found in the art, the amount of guidance set forth in the specification, the lack of correlatable working examples, the breadth of the claims, and the amount of experimentation required to practice the invention, it is concluded that one of skill in the art would have to practice undue experimentation in order to practice the invention.

7. Claims 1-25 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 9, and 23 recite "or corresponding to" in relation to DNA of a portion of a retroviral vector and "which is capable of infecting and directing expression". This recitation is indefinite. It is unclear as to what DNA "corresponding" to a vector is purported to be. Further,

it is not clear how one of skill in the art is to determine that this DNA has any specific capability unless it has been shown to actually have this property. The claims would be more clear if amended to recite "a portion of retroviral vector DNA comprising elements necessary for infection and direction of expression in target cells".

Claims 1, 2, 9, 23, and 25 recite "or a derivative thereof" in relation to the antimicrobial peptide. This recitation is indefinite because it is unclear as to what is encompassed by the claim. A derivative could include a peptide in which every residue has been changed. The term has no definition set forth in the specification. Therefore, it is unclear as to what applicants intend to claim.

Claims 1, 2, 9, and 23 recite the term "antimicrobial peptide". The term would reasonably be interpreted to mean a peptide which targets a microbe. However the claims indicate that the peptide is useful against tumor cells and, in claim 23, for correcting a genetic defect. Therefore, it is not clear exactly what peptides are encompassed by the claimed invention. The definition set forth in the specification does not clearly define the term (see page 9 lines 5-12). Therefore, one of skill in the art is not reasonably apprised as to the scope of the invention.

Claims 1, 2, 9, 23, and 25 recite "treatment". This term renders the claims indefinite because the art provides no definite interpretation and the term is not defined in the specification. The term may be interpreted as providing therapy by some or as merely supplying some effect by others. Therefore, one of skill in the art is not reasonably apprised of the scope of the claimed invention.

Claim 2 is indefinite because the claim begins "the recombinant vector" and later recites "said coding sequences" without providing any antecedent basis for either recitation. It seems as though applicants may have intended to make the claim dependent upon claim 1. The claim should be amended to provide antecedent basis to the recited recitations.

Claim 11 is indefinite because the claim recites the claim from which it depends 2 times and refers to parts of the claim and not the invention of the claim. The claim recites "a retroviral particle produced by" indicating that the claim should depend upon a method or process claim in which following the steps of the claim would lead to the particle claimed here. Therefore, it is not clear as to what applicants are intending to claim.

Claims 17 and 18 provide for the use of the vector of claim 1, or the vector system of claim 9, respectively, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use without any active, positive steps delimiting how this use is actually practiced.

Claims 17 and 18 are rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim 22 is indefinite because the claim is directed to a host cell without reciting that the cell is isolated or cultured. Therefore, the claim reads upon the entire host. It is, therefore, unclear as to whether applicants intend to claim cells or a host.

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. Claims 1-15, 17-19, and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper et al., WO 95/01095 in view of Gunzburg et al., WO 96/07748.

The direction of the claims is discussed above. It is noted that claim 19 is directed to a pharmaceutical composition. This recitation is an intended use of the composition. The main component of the composition is the particle of claim 11, therefore, no further limitations is given weight in claim 19. Claims 17-18 are directed to a use of the vector of claim 1 or the vector system of claim 9, respectively. No steps are set forth in the claim, just an intended use. Therefore, no further limitations are given weight in claims 17-18.

Cooper et al. teach transposon-based vectors comprising sequences encoding lytic peptides. The lytic peptides include melittins, magainins, defensin, cecropins, etc. (see abstract). Cooper et al. teach that genes coding for lytic peptides can be transferred and stably expressed in

mammalian, vertebrate, and animal cells (see page 10, lines 26-28). Populations of cells were transformed with the vector including the making of transgenic catfish. The transposon based vector was used because it enhances the integration of DNA into eukaryotic cells without relying on homologous recombination or microinjection (see page 11, lines 13-20). Cooper et al. do not teach the use of a retroviral vector or a vector comprising DNA of a portion of a retroviral vector.

Gunzburg et al. teaches promoter conversion retroviral vectors (see abstract). The vector comprises a 5' LTR consisting of U3-R-U5, a coding sequence, and a 3' LTR wherein the U3 or a portion thereof has been deleted and replaced with a polylinker, followed by R-U5 (see abstract). Preferably the polylinker carries at least one unique restriction said and at least one insertion of a heterologous DNA fragment (see page 6, lines 4-8). The regulatory elements and promoters are preferably regulatable by transacting molecules (see page 6). The coding sequences are preferably antiviral genes, antitumor genes, or therapeutic genes (see page 7). A packaging cell line is also disclosed (see page 7). The mRNA of the provirus and the provirus is disclosed (see page 8). Gunzburg et al. do not teach that the coding sequences encode antimicrobial peptides.

Retroviruses are well known and widely used in the art as a vector for transferring genes into eukaryotic cells. The skill level in the art of molecular biology is very high. Gunzberg et al. teach that the vectors disclosed in '748 have superior qualities thereby motivating one of skill in the art to substitute the retroviral vectors in place of the transposon based vectors to transfer, express, and produce lytic peptides in eukaryotic cells. Therefore, it would have been *prima facie* obvious at the time the invention was made to make and use a retroviral vector, which is U3- in

the 3' LTR in which a polylinker is inserter in its place, comprising coding sequences encoding lytic peptides.

It is noted that applicants may overcome the instant rejection by perfecting the priority claim (see above).

10. Claims 1-15, 17-19, and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooper et al. in view of Temin et al., US 5,124,263 or Gilboa, US 5,658,775.

The direction of the claims is discussed above.

The teaching of Cooper et al. is discussed above.

Temin et al. teach a system for growing stocks of replication incompetent retrovirus (see abstract). The system has much less risk of recombination events in the helper (packaging) cell (see abstract). A particularly preferred vector in JD220SVHy as depicted in Figure 5 (see col. 5, lines 19-40). The vector has a deletion in the 3' U3 region. Also a polylinker with a unique XhoI site is inserted in it's place. (Temin et al. do not fully describe the construction of the vector, but instead cite Dougherty et al. which does fully describe the construction. A copy of Dougherty et al. is included for applicant's convenience.) Helper cells are also described for the production of the retroviral particles. Temin et al. teach that this system is superior because it makes reduces risk of recombination, reduces risks of producing replication competent virus, and makes the vectors useful in a broader hose range (see section bridging cols. 2-3). Temin et al. do not suggest inserting coding sequences which code for antimicrobial peptides, nor do they teach that any other heterologous sequence would be inserted into the U3 region.

Gilboa teaches double copy retroviral vectors. A gene is inserted into the 3' U3 region such that when transcribed, the gene also appears in the 5' U3 region (see figure published on front page of patent, and col. 5, lines 60-67). Gilboa teaches that a second gene can be inserted between the LTRs (see figures 5B and 9, and col. 9, lines 31-38). Portions of the U3 region may also be deleted (see figure 10, and col. 9, lines 53-55). The gene inserted into the U3 region may also have an internal promoter (see col. 9, lines 1-5). Packaging cells and production of virion particles is disclosed (see col. 6, lines 1-7). Cells were infected with the virion produced from the packaging cells (see cols. 12-15). Gilboa does not teach that the non-selectable gene inserted between the LTRs would be a coding sequence encoding antimicrobial peptides. Nor does he teach that a polylinker comprising a unique restriction site was inserted into the U3 region, however, it is likely that this was done as polylinkers comprising unique restriction sites are routinely inserted into vectors to allow ease in cloning. Given that Gilboa inserted genes into the U3 region, he likely also inserted a unique site.

Retroviruses are well known and are widely used to transfer genes into eukaryotic cells. The level of skill in the art of molecular biology is very high. Both Gilboa and Temin et al. suggest that the disclosed vectors are superior vectors for transferring genes to eukaryotic cells. One of skill in the art would be motivated to use the retroviral vectors as disclosed by Temin et al. or Gilboa to transfer lytic peptides to eukaryotic cells as demonstrated by Cooper et al., but using another vector system. Therefore, it would have been prima facie obvious at the time the invention was made to substitute retroviral vectors as taught by Temin et al. or Gilboa in place of

the transposon based vectors used by Cooper et al. to transfer coding sequences encoding lytic peptides to eukaryotic cells.

Conclusion

11. No claim is allowed.

12. Claims 16 and 23-25 are free of the prior art of record because the prior art did not teach or fairly suggest using a retroviral vector comprising a sequence encoding an antimicrobial peptide in an animal *in vivo* to treat viral, fungal, bacterial, or tumor diseases.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Clark whose telephone number is (703) 305-4051. The examiner can normally be reached on Mondays-Fridays from 7:10 a.m. EST to 3:40 p.m. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brian Stanton, can be reached on (703) 308-2801. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DRC

03/12/99